As expected, DMI reduced NE uptake activity in both SHAM and CHF animals, but its actions on TH differed between the two groups. While it exerted no effect on TH in SHAM animals, DMI reduced the decrease in TH that occurred in CHF. The results suggest that the cardiac sympathetic changes that occur in CHF may be caused by excessive NE, and that the neurotoxic effect of NE on TH involves the NE reuptake mechanism.

4:45

809-4 Effect of Beta Adrenergic Stimulation on Regional Norepinephrine Spillover in Human Congestive Heart Failure

Steven R. Goldsmith, Michael Garr *Hennepin County Medical Center and the University of Minnesota, Minneapolis, MN*

Beta blockers may be effective therapy in congestive heart failure; the reasons are not fully clear. Presynaptic beta-1 receptors are known to facilitate norepinephrine (NE) release. If this effect occurs in congestive heart failure (CHF) an important positive feedback loop might exist contributing to chronic sympathetic activation; conversely, interference with such an interaction could contribute to beneficial effects of beta adrenergic blockade. To test the hypothesis that beta simulation would lead to increased local sympathetic activity we measured regional forearm NE kinetics (clearance method of Esler with ^{3}HNE) during intraarterial infusion of subsystemic doses of isoproterenol (ISU) in 6 patients with chronic stable, moderate CHF. As a control for flow-related effects due to vasodilation from ISU, we also assessed the response to nitroprusside (NP). Forearm blood flow (FBF) and regional NE spillover (Regional NE s/o = $[NE_a - NE_v] + NE_a$ [extraction ^{3}HNE] × FBF) were:

	Control	ISU	Recontrol	NP
FBF (ml/100 gm/min)	1.5 ± 1.17	4.6 ± 1.0*	1.8 ± 0.32	6.5 ± 1.5*
NE s/o (pg/min)	447 ± 115	1276 ± 425*	420 ± 121	983 ± 389

*$p < 0.01$ vs. Control or Recontrol

Regional NE s/o therefore increased after local infusion of isoproterenol, but not after a similar increase in flow during nitroprusside. Although a flow-dependent effect is not completely excluded, these data suggest that regional beta adrenergic stimulation is capable of increasing local NE s/o. This observation may be relevant to both the control of sympathetic activity and the possible effects of beta blockers in CHF.

810 Mechanisms and Altering Growth of Thrombus

Wednesday, March 22, 1995, 4:00 p.m.–5:00 p.m.
Ernest N. Morial Convention Center, Room 21

4:00

810-1 Enhanced Inflammatory Acute Phase Response After Percutaneous Coronary Angioplasty in Patients with Unstable Angina

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Elevated levels of C-reactive protein (CRP), a sensitive marker of inflammation, are independent predictors of short-term prognosis in patients (pts) with unstable angina (UA). The causes of the acute phase response in UA, however, are still unknown. Percutaneous transluminal coronary angioplasty (PTCA) is an useful model for the assessment of the effects of plaque disruption and myocardial ischemia on the acute phase response. Serum levels of CRP were measured in 21 pts with chronic stable angina (SA) (G1) and in 22 pts with UA refractory to maximal medical treatment (G2), undergoing single-vessel PTCA. Venous blood samples were taken immediately before PTCA and 6, 24, 48, 72 hours after the end of the procedure. CRP values are expressed as median and range.

Results. Before PTCA, CRP was elevated (>3 mg/l) in 2/21 G1 pts (10%) and in 16/22 G2 pts (73%) ($p < 0.001$): it was 2.4 (2–4.4) mg/l in G1 and 8 (2.4–29) mg/l in G2 ($p < 0.001$). After PTCA, CRP increased to a peak value of 2.6 (2–16.4) mg/l 38 ± 13 hrs after the procedure in G1, and to a peak value of 19.9 (2.8–49.4) mg/l 32 ± 14 hrs after the procedure in G2 ($p < 0.001$, G1 vs G2). A significant increase in CRP after PTCA, defined as an increase >50% the basal values, was observed in 8/21 G1 pts and in 16/22 G2 pts ($p < 0.05$). The percentage increase of CRP after PTCA was higher in G2 than in G1 (180 ± 239%, range 0–925% vs 118 ± 176%, range −13–489%, $p < 0.05$).

No difference in coronary stenosis severity before PTCA (84 ± 9% vs 89 ± 8%), residual stenosis (30 ± 7% vs 29 ± 10%), number of ballon inflations (6 ± 3.4 vs 5.3 ± 3.2), total inflation time (365 ± 202 vs 413 ± 197 sec) and mean inflation pressure (5 ± 0.9 vs 5 ± 1 atm) was found between G1 and G2 pts.

Conclusion: Our study shows that the plaque disruption and the brief periods of myocardial ischemia caused by PTCA elicit a variable individual inflammatory acute phase response, that is greater in UA compared to SA pts. These data suggest a higher inflammatory responsiveness in patients with UA, that may play a pathogenetic role in acute coronary syndromes, and help explaining the higher rate of acute complications typically observed in patients with unstable angina undergoing PTCA.

4:15

810-2 Thrombin Receptor Blockade on the Arterial Media Decreases Its Reactivity to Platelets and Neutrophils

Alvaro Moura, Jules Y.T. Lam, Glaci Letchacovski, Morley Hollenberg, John Dimaio *Montreal Heart Institute, Montreal, Quebec, Canada*

Thrombin receptor activating peptides have been shown to promote platelet activation by binding to platelet thrombin receptors. Recently, thrombin receptors on the vessel wall have also been described but their role or function is unclear. Expression of thrombin receptors on the injured arterial wall may be implicated in regulating vessel wall thrombogenicity and influencing mural thrombus formation. To assess the role of thrombin receptors on the thrombogenicity of the injured arterial wall, we examined the effect of a putative thrombin-receptor antagonist (TRAN) on platelet and neutrophil (PMN) deposition on porcine aortic media (simulating deeply injured arterial wall). The aortic media exposed to increasing concentration of TRAN were then placed in cylindrical flow chambers and exposed to circulating normal porcine blood at a shear rate of 3360 sec^{-1} for 5 min at 37°C. Quantitative ^{51}Cr platelet (× $10^6/cm^2$) and ^{111}In-neutrophil deposition (× $10^3/cm^2$) on the aortic media at various concentrations of TRAN (10^{-8} to 10^{-6} M) ($n = 6$ in each case) are shown below:

	Control	10^{-8} M	10^{-7} M	10^{-6} M
Platelet	133 ± 21	117 ± 28	107 ± 27	68 ± 16*
PMN	1176 ± 328	689 ± 188	728 ± 189	583 ± 160*

ANOVA, * $P < 0.05$ vs control

Conclusion: Inhibition of the thrombin receptor on the arterial media surface may inhibit the reactivity of the injured vessel wall to platelet and neutrophil accumulation. This may represent a novel mechanism of inhibiting arterial thrombus formation, and decreasing the thrombogenicity and inflammatory response of the injured arterial wall.

4:30

810-3 Thrombin and Thromboxane A_2 are both Important Mediators of Thrombus Formation Under Flow Conditions in Humans

Giovanni Melandri, Franco Semprini, Vittorio Cervi, Benedetta Descovich, Stefano Boschi, Angelo Branzi, Bruno Magnani. *Institute of Cardiology, University of Bologna, Italy*

Heparin (Hep) has been shown to be the first-line antithrombotic treatment in unstable angina, thus confirming that thrombin is a potent mediator of thrombus formation on deep vascular injury. Whether aspirin treatment may further add on the effects of heparin is controversial. To further elucidate the role of thrombin and thromboxane A_2 in this context, we investigated the effects of Hep at low (0.2–0.4 U/ml; Hep-L) and high (0.5–1.0 U/ml; Hep-H) concentrations and of Hep-L in presence of dual thromboxane inhibition/thromboxane A_2 receptor antagonism after the oral ingestion of Picotamide (PIC; 600 mg) in humans. We used a flow system allowing for native human blood to be exposed for 5 min to mild or deep vascular injury on porcine arterial segments. 111-In-labelled platelet deposition (PD × 10^6 / cm^2) was quantified on arterial segments in cylindrical (Badimon) flow chambers under low (212 s^{-1}) and high (1690^{-1}) shear rate at 37°C. PIC bioavailability was checked by measuring thromboxane B_2 synthesis by clotting human blood. Results (SEM):

	Hep-L	Hep-H	p	Hep-L + PIC	p
Mild injury (212 s^{-1})	1.6 (0.4)	0.6 (0.3)	*	0.7 (0.2)	*
Mild injury ($1690\ s^{-1}$)	3.9 (1.0)	2.2 (0.5)	*	1.8 (0.4)	*
Deep injury ($1690\ s^{-1}$)	12.4 (2.8)	8.2 (2.0)	§	6.8 (1.4)	§

*$p < 0.05$, §$p < 0.01$ vs Hep-L

Thus, thrombin is a strong mediator of thrombosis under flow conditions and requires high Hep levels. However a similar antithrombotic effect may be achieved by the combination of thromboxane A_2 blockade at the receptor level with low Hep levels.